REMARKS

Claims 1-4, 17-20 and 32-33 are currently under consideration.

Claims 5-16 and 21-31 have been cancelled without prejudice.

Claims 1-3 and 17-20 have been amended and claims 32-33 have been added.

Claims 1-3 and 17-20 have been amended to specify that the pharmaceutical composition comprises an inhibitor of human c-Src tyrosine kinase. Claims 3 and 19 have also been amended to eliminate AGL 1872 from the Markush group, since this material is the same as PP1. Support for these amendments can be found in the specification at page 16, lines 4-5, and in Fig. 3. No new matter is added by these amendments.

New claim 32 is dependent on claim 18 and specifies that the inhibitor is PP2. Support for this claim can be found in the Markush grouping of original claim 18.

New claim 33 is dependent on claim 3 and specifies that the inhibitor is PP2. Support for this claim can be found in the Markush grouping of original claim 3.

No new matter is added by these new claims.

Claims 1, 2, and 17-18 stand rejected under 35 USC 102(e) as allegedly being anticipated by US 6,001,839 ("Calderwood Patent"). The Calderwood Patent teaches that certain pyrrolopyrimidine compounds, not pyrazolopyrimidine compounds, are useful for treating VEGF mediated edema. This patent only generally mentions the Src family of tyrosine kinases along with other classes of kinases (i.e., the Syk and Janus families, at col. 12, line 53 through col. 13, line 9). The present claims are limited to methods and articles of manufacture including inhibitors of human c-Src, a specific member of the Src family of tyrosine kinases. In the portion of the patent that discusses determination of the *in vitro* potency of the pyrrolopyrimidine inhibitors (col. 18, line 28 through col. 19, line 18), the Calderwood Patent teaches an assay for Lck (a Src family inhibitor) and Zap (a Syk family inhibitor), but does not mention human c-Src. The Calderwood Patent does not teach or suggest that the pyrrolopyrimidine compounds are inhibitors of human c-Src. The selectivity of tyrosine kinase inhibitors is highly unpredictable with large variability in selectivities and activities depending on the spacial arrangement of substituents (see, for example, McMahon

et al., Current Opin. in Drug Discov.& Devel., 1998; 1(2):131-146, particularly at page 142 under heading "Summary and outlook", a copy of which is attached hereto).

Furthermore, the Calderwood Patent is not enabling for a method of ameliorating tissue damage related to vascular leakage or edema comprising contacting said tissue with a vascular permeability modulating amount of a pharmaceutical composition comprising a human c-Src tyrosine kinase inhibitor, as claimed in the present application. The Calderwood Patent merely contains a *general* teaching that the compounds are tyrosine kinase inhibitors, and specifically teaches that certain of the compounds are Lck inhibitors (col. 19, lines 12-14). The patent states that the pyrrolopyrimidines may useful in treatment of "VEGF mediated edema", but provides no teaching whatsoever that an inhibitor of human c-Src would have such utility. No activity data are presented in this patent for any of the inhibitors disclosed, against any tyrosine kinase. There is nothing in the patent that would enable one of ordinary skill to practice the methods and articles of manufacture claimed in the present application. Accordingly, the Calderwood Patent is not enabling for the methods and articles of manufacture of claims 1, 2, 17 and 18.

For the reasons stated above, the Calderwood Patent does not anticipate claims 1, 2, 17 or 18. This ground for rejection should be withdrawn.

Claims 1, 2, and 17-18 stand rejected under 35 USC 102(e) as allegedly being anticipated by US Patent Application No. 2003/0187001 ("Calderwood Application"). The Calderwood Application teaches that certain pyrrolopyrimidine compounds are useful for treating VEGF mediated edema at paragraph 101, however it does not teach that inhibitors of human c-Src have such activity. Rather, paragraph 101 states that *KDR* tyrosine kinase are useful for inhibiting vascular permeability and edema.

In paragraph 53, this application only generally mentions the Src family of tyrosine kinases along with other classes of kinases (i.e., the Syk, Tec, Csk, Jak, Map, and Nik families). In paragraph 53, the examples of Src kinases listed in the parenthesis are Ick [sic], blk and lyn, but not human c-Src. Similarly, the laundry list of kinases in paragraph 111 lumps Src together with at least six other families of inhibitors.

The present claims are limited to methods and articles of manufacture including inhibitors of human c-Src, which is not mentioned in the Calderwood Application.

In the portion of the patent that discusses determination of the *in vitro* potency of the pyrrolopyrimidine inhibitors (col. 18, line 28 through col. 19, line 18), the Calderwood Application teaches an assay for Lck (a Src family inhibitor) and Zap (a Syk family inhibitor), but does not mention human c-Src. The Calderwood Application does not teach or suggest that the pyrrolopyrimidine compounds are inhibitors of human c-Src as required by all of the present claims. The selectivity of tyrosine kinase inhibitors is highly unpredictable with large variability in selectivities and activities depending on the spacial arrangement of substituents (see, for example, McMahon *et al.*, discussed above).

Additionally, the Calderwood Application is not enabling for a method of ameliorating tissue damage related to vascular leakage or edema comprising contacting said tissue with a vascular permeability modulating amount of a pharmaceutical composition comprising a human c-Src tyrosine kinase inhibitor, as claimed in the present application. The Calderwood Application merely contains a *general* teaching that the compounds are tyrosine kinase inhibitors, and specifically teaches that certain of the compounds are *KDR* inhibitors that can be used to treat edema (paragraph 101), not inhibitors of human c-Src, as required by all of the present claims. No activity data are presented in this application for any of the inhibitors disclosed in the application, against any tyrosine kinase. There is nothing in the application that would enable one of ordinary skill to practice the methods and articles of manufacture claimed in the present application.

Accordingly, the Calderwood Application does not anticipate claims 1, 2, 17 or 18, and this ground for rejection also should be withdrawn.

Claims 1, 2, and 17-18 stand rejected under 35 USC 102(e) as allegedly being anticipated by US Patent Application No. 2002/0156081 ("Hirst *et al.*"), as well. Like the Calderwood Patent and the Calderwood Application, Hirst *et al.* does not provide an enabling disclosure of the presently claimed invention. Treatment of edema is discussed only generally in a laundry list of application in paragraph 315 of Hirst *et al.* In paragraph 350, the application states that some of the compounds can be used to treat edema. Of the over 950 examples of compounds presented in Hirst *et al.* there is not a single data point of inhibition data. Only general allusions to unspecific activity against various diverse classes of tyrosine kinases are provided, as in paragraphs 311. There is no specific teaching in Hirst *et al.* that an

inhibitor of human c-Src can be used to treat vascular leakage and edema, as required by all of the present claims. Accordingly, Hirst *et al.* cannot anticipate claims 1, 2, 17 or 18.

Claims 3, 4, 19 and 20 stand rejected as being obvious over the Calderwood Patent, the Calderwood Application, and Hirst *et al.* in view of Hanke *et al.* Claims 3 and 4 are directly of indirectly dependent on claims 1 and 2, as is new claim 32. Claims 19 and 20 are either directly or indirectly dependent on claims 17 and 18, as is new claim 33. Neither the Calderwood Patent, the Calderwood Application, nor Hirst *et. al.* disclose the invention of claims 1, 2, 17 and 18, as noted above. Moreover, none of these references disclose the pyrazolopyrimidine inhibitors PP1 and PP2, which are required by claims 3, 4, 19, 20, 32 and 33. Hanke *et al.*, while disclosing PP1 and PP2, does not disclose treatment of vascular leakage and edema utilizing an inhibitor of human c-Src as required by the present claims. Hanke does demonstrate that one inhibitor can have a wide variance in activity against different tyrosine kinases (see Table I on page 698). Hanke *et al.* would not have provided any motivation whatsoever to one of ordinary skill to use PP1 or PP2 to ameliorate tissue damage due to edema or vascular permeability as taught by the Calderwood and Hirst references. At most, the teachings of Hanke *et al.* are but an invitation to experiment that does not vitiate patentability.

It is argued in the Office Action that there is a structural similarity between the compounds disclosed in the Calderwood Patent and Calderwood Application to PP1 and PP2, and that this structural similarity would have motivated one of skill in the art to use PP1 and PP2 to treat edema as described in the Calderwood references and Hirst *et al.* The alleged structural similarity between the Calderwood compounds and PP1/PP2 is superficial at best. As is evident from Hanke *et al.* and McMahon *et al.* discussed above, inhibition of tyrosine kinases is highly unpredictable. Small changes in structure can lead to large changes in activity and selectivity. The compounds of the Calderwood references are pyrrolopyrimidines, whereas PP1 and PP2 are pyrazolopyrimidines. The additional nitrogen in PP1 and PP2 relative to the Calderwood compounds could have a significant effect on activity and selectivity. In addition, the Calderwood compounds have a bulky phenoxy substituent on the phenyl ring, whereas PP1 and PP1 have relatively small methyl and chloro substituents on the phenyl ring. These differences could have significant effects on the

binding affinity and selectivity of the inhibitors, particularly since the compounds bind to specific binding pockets in the enzymes (see McMahon *et al.*, page 135, paragraph bridging column 1 and column 2). Accordingly, one of ordinary skill in the art would not have a reasonable expectation of success in using PP1 and PP2 of Hanke *et al.* to treat edema as disclosed in the Calderwood and Hirst references.

For the foregoing reasons, none of the presently pending claims are either anticipated or rendered obvious by the applied references. Reconsideration and early allowance of all claims is earnestly solicited.

Respectfully submitted,

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